## THE CLAIMS

**We claim:**

1. A method of reducing, treating or preventing drug-mediated respiratory depression in an animal, incident to the administration to said animal of a respiratory depression-mediating drug, comprising administering to the animal receiving said drug an effective amount of a delta receptor agonist compound.

2. A method according to claim 1, wherein the delta agonist also exhibits mu receptor agonist character.

3. A method according to claim 1, wherein said delta receptor agonist is administered with a separate mu receptor agonist compound.

4. A method according to claim 1, wherein the delta agonist is selected from the group consisting of:

(-)-4-((αR)-α-((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

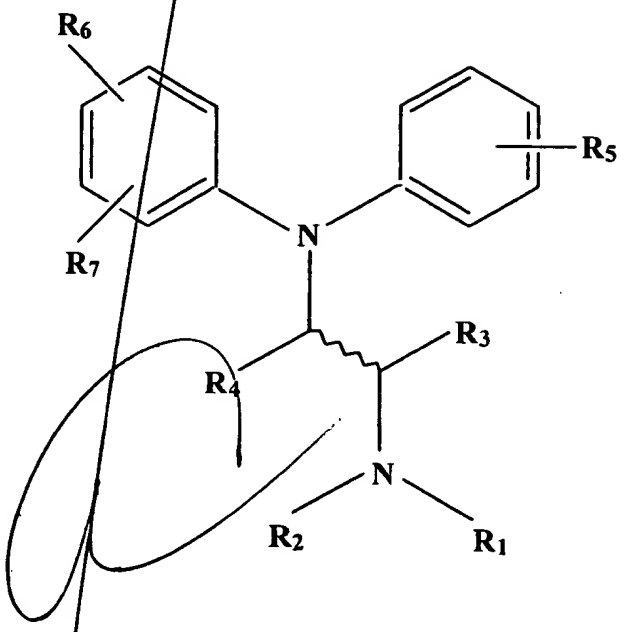
(-)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide,

deltorphin I;

deltorphin II; and

[D-Pen$^2$,D-Pen$^5$]-enkephalin.

5. A method according to claim 1, wherein said delta agonist comprises a compound of the formula:




in which,

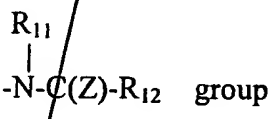
$R_1$ and $R_2$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{3-7}$ cycloalkenyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, $C_{3-5}$ alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a $C_{3-7}$ alkyl ring which may be interrupted by oxygen.

$R_3$ and $R_4$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl, or $R_4$ is oxygen forming with the carbon atom to which is attached a C=O group;

$R_5$ is hydrogen, hydroxy, $C_{1-3}$ alkoxy, thiol or alkylthio;

$R_6$ is phenyl, halogen, $NH_2$ or a para or meta -C(Z)-$R_8$ group, in which Z is oxygen or sulphur;

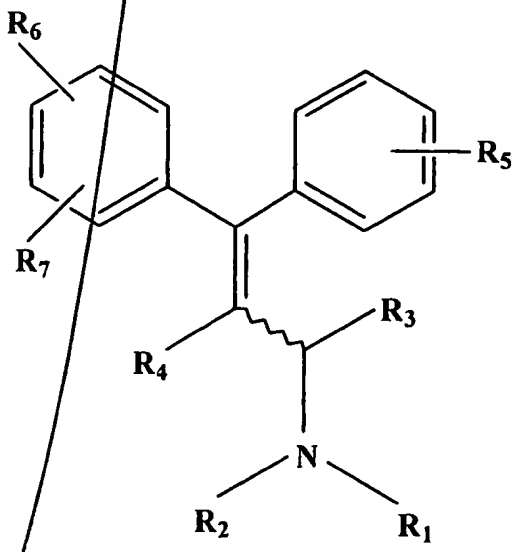
$R_8$ is $C_{1-8}$-alkyl, $C_{1-8}$-alkoxy or $NR_9R_{10}$, wherein $R_9$ and $R_{10}$, which may be the same or different, are hydrogen, straight or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, aryl or aralkyl,

or $R_6$ is a para or metal  group

in which $R_{11}$ and $R_{12}$ which may the same or different are hydrogen, straight or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

$R_7$ is hydrogen, straight or branched $C_{1-8}$ alkyl or halogen.

6. A method according to claim 1, wherein said delta agonist comprises a compound of the formula:



in which,

$R_1$ and $R_2$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{3-7}$ cycloalkenyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, $C_{3-5}$ alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a $C_{3-7}$ alkyl ring which may be interrupted by oxygen.

$R_3$ and $R_4$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl;

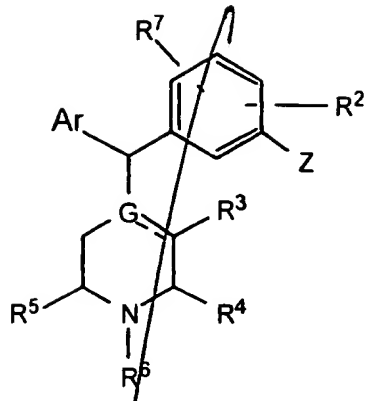
$R_5$ is hydroxy, $C_{1-6}$ alkoxy, thiol or alkylthio;

$R_6$ is a -C(Z)-Rg group, in which Z is oxygen or sulphur, $R_8$ is $C_{1-8}$-alkyl, $C_{1-8}$-alkoxy or $NR_9R_{10}$, wherein $R_9$ and $R_{10}$, which may be the same or different, are hydrogen, straight or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, aryl or aralkyl,

or $R_6$ is a $-N(R_{11})-C(Z)-R_{12}$ group

in which $R_{11}$ and $R_{12}$ have the same meaning as $R_9$ and $R_{10}$ or together form an optionally substituted heterocyclic ring and Z is as defined above, and $R_7$ is hydrogen, straight or branched $C_{1-8}$ alkyl or halogen.

7. A method of reducing, treating or preventing drug-mediated respiratory depression in an animal, comprising administering to the animal an effective amount of a compound of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent $R^1$,

Y is selected from the group consisting of:

hydrogen;

halogen;

$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;

$C_1$-$C_6$ haloalkyl;

$C_1$-$C_6$ alkoxy;

$C_3$-$C_6$ cycloalkoxy;

sulfides of the formula $SR^8$ where $R^8$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_6$ cycloalkyl, arylalkyl having a $C_5$-$C_{10}$ aryl moiety and an $C_1$-$C_6$ alkyl moiety, or $C_5$-$C_{10}$ aryl;

sulfoxides of the formula $SOR^8$ where $R^8$ is the same as above;

sulfones of the formula $SO_2R^8$ where $R^8$ is the same as above;

nitrile;

$C_1$-$C_6$ acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where $R^8$ is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where $R^9$ and $R^{10}$ may be the same or different, and may be hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_2$-$C_6$ hydroxyalkyl, $C_2$-$C_6$ methoxyalkyl, $C_3$-$C_6$ cycloalkyl, or $C_5$-$C_{10}$ aryl, or $R^9$ and $R^{10}$ together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above, or $C_2$-$C_{30}$ peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

$R^1$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

$R^2$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

$R^3$, $R^4$ and $R^5$ may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of $R^3$, $R^4$ or $R^5$ is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of $R^3$, $R^4$ and $R^5$ together may form a bridge of 1 to 3 carbon atoms;

$R^6$ is selected from the group consisting of:

hydrogen;

$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;

$C_3$-$C_6$ cycloalkyl;

arylalkyl having $C_5$-$C_{10}$ aryl and $C_1$-$C_6$ alkyl moieties;

alkoxyalkyl having $C_1$-$C_4$ alkoxy and $C_1$-$C_4$ alkyl moieties;

$C_2$-$C_4$ cyanoalkyl;

$C_2$-$C_4$ hydroxyalkyl;

aminocarbonylalkyl having a $C_1$-$C_4$ alkyl moiety; and

$R^{12}COR^{13}$, where $R^{12}$ is $C_1$-$C_4$ alkylene, and $R^{13}$ is $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkoxy; and

$R^7$ is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof.

8. A method according to claim 7, wherein Ar is a 6-member carbocyclic aromatic (benzene) ring and $R^1$ is hydrogen.

9. A method according to claim 7, wherein Y is a carboxamide of the formula $CONR^9R^{10}$.

10. A method according to claim 9, wherein $R^9$ and $R^{10}$ together form a ring of five or six atoms, thereby forming a pyrrolidinyl or piperidino ring.

11. A method according to claim 9, wherein $R^9$ and $R^{10}$ are the same or different and are each independently selected from hydrogen, $C_1$ alkyl and $C_2$ alkyl.

12. A method according to claim 8, wherein Y is hydrogen.

13. A method according to claim 8, wherein Y is a sulfone of the formula $SO_2R^8$, and $R^8$ is $C_1$-$C_6$ alkyl.

14. A method according to claim 8 wherein G is N, $R^7$ and $R^2$ are each hydrogen, and Z is hydroxyl.

15. A method according to claim 8, wherein $R^6$ is selected from the group consisting of hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl and $C_2$-$C_6$ alkynyl.

16. A method according to claim 9, wherein $R^6$ is selected from the group consisting of hydrogen, methyl, propyl, allyl and butenyl.

17. A method according to claim 14, wherein $R^3$, $R^4$ and $R^5$ are hydrogen or methyl, where the total number of methyl groups is one or two.

18. A method according to claim 7, wherein $R^3$ and $R^5$ are both methyl, and $R^4$ is hydrogen.

19. A method according to claim 7 wherein the compound is selected from the group consisting of:

(-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(-)-4-((αR)-α-((2R,5R)-2,5-dimethyl-4-propyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

4-((αR)-α-(2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

N,N-diethyl-4-((αR)-3-hydroxy-α-((2R,5R)-2,5-dimethyl-1-piperazinyl)benzyl)benzamide;

4-((αR)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-methyl-benzamide;

3-((αR)- α-((2S, 5S)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-N,N-diethyl-4-((αR*)-3-hydroxy-α-((2R*,5S*)-2,4,5-trimethyl-1-piperazinyl)benzyl)-benzamide;

(+)-4-((αS)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

3-((αR)-4-(piperidinocarbonyl)- α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

3-((αR)-4-(1-pyrrolidinylcarbonyl)-α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

(±)-3-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-4-(methylsulfonyl)benzyl)-phenol;

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfon-amide; or

(-)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide,

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-4-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxbenzyl)benzamide;

(±)-4-((αR*)-α-((2R*,5S*)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

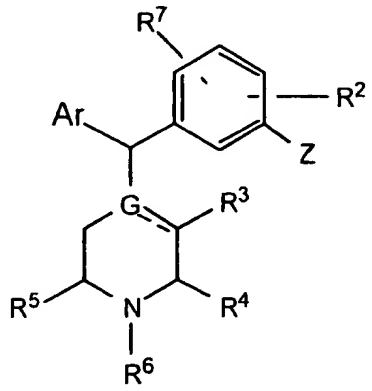
(±)-cis-4-(α-(4-allyl-3,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

cis-4-(α-(3,5-dimethyl-4-(methylallyl)-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

and pharmaceutically acceptable salts thereof.

20. A method according to claim 19, wherein the compound is (-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide or a pharmaceutically acceptable salt thereof.

21. A method for screening opioid respiratory depression-suppressing compounds, comprising conducting activity reversal assays of a candidate respiratory depression-suppressing compound in receptor tissue to determine if the candidate respiratory depression-suppressing compound transductionally mediates a respiratory depression effect in the receptor tissue, in response to a respiration-depressing composition, wherein said activity reversal assays are conducted comparatively, in the absence and in the presence of an anti-suppression compound of the formula




(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent $R^1$,

Y is selected from the group consisting of:

hydrogen;

halogen;

$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;

$C_1$-$C_6$ haloalkyl;

$C_1$-$C_6$ alkoxy;

$C_3$-$C_6$ cycloalkoxy;

sulfides of the formula $SR^8$ where $R^8$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_6$ cycloalkyl, arylalkyl having a $C_5$-$C_{10}$ aryl moiety and an $C_1$-$C_6$ alkyl moiety, or $C_5$-$C_{10}$ aryl;

sulfoxides of the formula $SOR^8$ where $R^8$ is the same as above;

sulfones of the formula $SO_2R^8$ where $R^8$ is the same as above;

nitrile;

$C_1$-$C_6$ acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where $R^8$ is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where $R^9$ and $R^{10}$ may be the same or different, and may be hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_2$-$C_6$ hydroxyalkyl, $C_2$-$C_6$ methoxyalkyl, $C_3$-$C_6$ cycloalkyl, or $C_5$-$C_{10}$ aryl, or $R^9$ and $R^{10}$ together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above, or $C_2$-$C_{30}$ peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above;

Z is selected from the group consisting of:
hydroxyl, and esters thereof;
hydroxymethyl, and esters thereof; and
amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

$R^1$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

$R^2$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

$R^3$, $R^4$ and $R^5$ may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of $R^3$, $R^4$ or $R^5$ is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of $R^3$, $R^4$ and $R^5$ together may form a bridge of 1 to 3 carbon atoms;

$R^6$ is selected from the group consisting of:
hydrogen;
$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;
$C_3$-$C_6$ cycloalkyl;
arylalkyl having $C_5$-$C_{10}$ aryl and $C_1$-$C_6$ alkyl moieties;
alkoxyalkyl having $C_1$-$C_4$ alkoxy and $C_1$-$C_4$ alkyl moieties;
$C_2$-$C_4$ cyanoalkyl;
$C_2$-$C_4$ hydroxyalkyl;
aminocarbonylalkyl having a $C_1$-$C_4$ alkyl moiety; and
$R^{12}COR^{13}$, where $R^{12}$ is $C_1$-$C_4$ alkylene, and $R^{13}$ is $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkoxy; and

$R^7$ is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof,

to determine if the activity of the candidate compound is substantially reversed at the tissue site by the presence of the anti-suppression compound of formula (I), thereby indicating the candidate respiratory depression-suppressing compound as possessing potential bioefficacy for supressing respiratory depression effects incident to the use of other therapeutic agents.

22. A method according to claim 21, wherein the anti-suppression compound of formula (I) is selected from the group consisting of:

(-)-4-((αS)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(-)-4-((αS)-α-((2R,5R)-2,5-dimethyl-4-propyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide; and

*cis*-4-(α-(4-((Z)-2-butenyl)-3,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide; and

acceptable salts thereof.

23. A pharmaceutical composition comprising:

(1) an effective amount of a bioactive compound mediating respiratory depression, muscle rigidity, and/or nausea/vomiting as an unwanted side effect thereof; and

(2) a delta receptor agonist.

24. A pharmaceutical composition comprising:

(1) an effective amount of a bioactive compound mediating respiratory depression, muscle rigidity, and/or nausea/vomiting as an unwanted side effect thereof; and

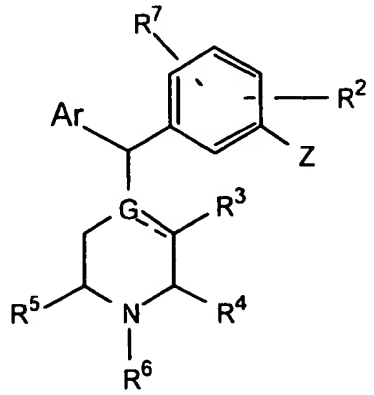
(2) a delta receptor agonist selected from the group consisting of:

I. [D-Pen$^2$,D-Pen$^5$]-(enkephalin);

II. deltorphin I;

III. deltorphin II;

IV. delta agonist compounds of the formula:




(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent $R^1$,

Y is selected from the group consisting of:

hydrogen;

halogen;

$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;

$C_1$-$C_6$ haloalkyl;

$C_1$-$C_6$ alkoxy;

$C_3$-$C_6$ cycloalkoxy;

sulfides of the formula $SR^8$ where $R^8$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_6$ cycloalkyl, arylalkyl having a $C_5$-$C_{10}$ aryl moiety and an $C_1$-$C_6$ alkyl moiety, or $C_5$-$C_{10}$ aryl;

sulfoxides of the formula $SOR^8$ where $R^8$ is the same as above;

sulfones of the formula $SO_2R^8$ where $R^8$ is the same as above;

nitrile;

$C_1$-$C_6$ acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where $R^8$ is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where $R^9$ and $R^{10}$ may be the same or different, and may be hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_2$-$C_6$ hydroxyalkyl, $C_2$-$C_6$ methoxyalkyl, $C_3$-$C_6$ cycloalkyl, or $C_5$-$C_{10}$ aryl, or $R^9$ and $R^{10}$ together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above, or $C_2$-$C_{30}$ peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;
hydroxymethyl, and esters thereof; and
amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

$R^1$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

$R^2$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

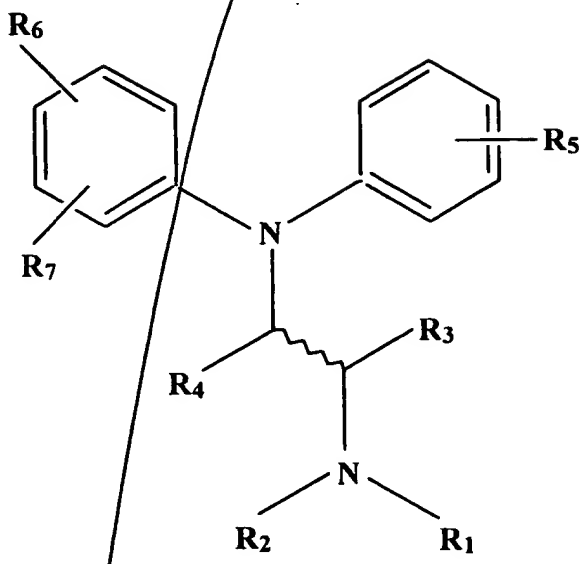
$R^3$, $R^4$ and $R^5$ may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of $R^3$, $R^4$ or $R^5$ is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of $R^3$, $R^4$ and $R^5$ together may form a bridge of 1 to 3 carbon atoms;

$R^6$ is selected from the group consisting of:
hydrogen;
$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;
$C_3$-$C_6$ cycloalkyl;
arylalkyl having $C_5$-$C_{10}$ aryl and $C_1$-$C_6$ alkyl moieties;
alkoxyalkyl having $C_1$-$C_4$ alkoxy and $C_1$-$C_4$ alkyl moieties;
$C_2$-$C_4$ cyanoalkyl;
$C_2$-$C_4$ hydroxyalkyl;
aminocarbonylalkyl having a $C_1$-$C_4$ alkyl moiety; and
$R^{12}COR^{13}$, where $R^{12}$ is $C_1$-$C_4$ alkylene, and $R^{13}$ is $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkoxy; and

$R^7$ is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof;

V. delta agonist compounds of the formula:




in which,

$R_1$ and $R_2$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{3-7}$ cycloalkenyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, $C_{3-5}$ alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a $C_{3-7}$ alkyl ring which may be interrupted by oxygen.

$R_3$ and $R_4$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl, or $R_4$ is oxygen forming with the carbon atom to which is attached a C=O group;

$R_5$ is hydrogen, hydroxy, $C_{1-3}$ alkoxy, thiol or alkylthio;

$R_6$ is phenyl, halogen, $NH_2$ or a para or meta -C(Z)-$R_8$ group, in which Z is oxygen or sulphur;

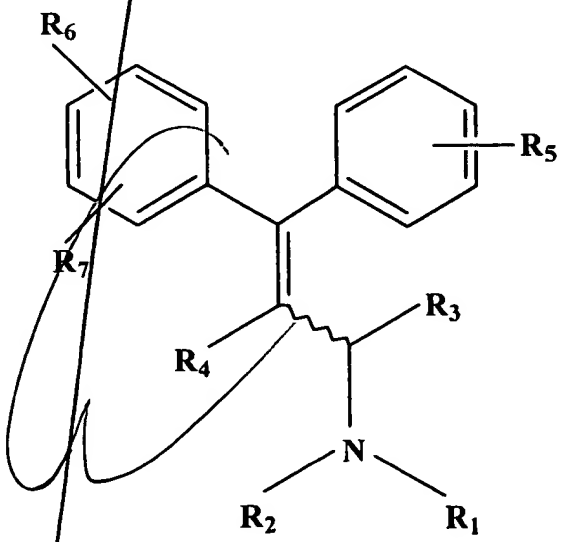
$R_8$ is $C_{1-8}$-alkyl, $C_{1-8}$-alkoxy or $NR_9R_{10}$, wherein $R_9$ and $R_{10}$, which may be the same or different, are hydrogen, straight or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, aryl or aralkyl,

or $R_6$ is a para or metal $-N-C(Z)-R_{12}$ group ($R_{11}$)

in which $R_{11}$ and $R_{12}$ which may the same or different are hydrogen, straight or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

$R_7$ is hydrogen, straight or branched $C_{1-8}$ alkyl or halogen; and

VI. delta agonist compounds of the formula:




in which,

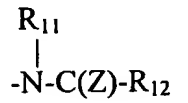
$R_1$ and $R_2$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{3-7}$ cycloalkenyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, $C_{3-5}$ alkynyl, aryl,

aralkyl or furan-2 or 3-yl alkyl or may form together a $C_{3-7}$ alkyl ring which may be interrupted by oxygen.

$R_3$ and $R_4$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl;

$R_5$ is hydroxy, $C_{1-6}$ alkoxy, thiol or alkylthio;

$R_6$ is a -C(Z)-Rg group, in which Z is oxygen or sulphur, $R_8$ is $C_{1-8}$-alkyl, $C_{1-8}$-alkoxy or $NR_9R_{10}$, wherein $R_9$ and $R_{10}$, which may be the same or different, are hydrogen, straight or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, aryl or aralkyl,

or $R_6$ is a  group

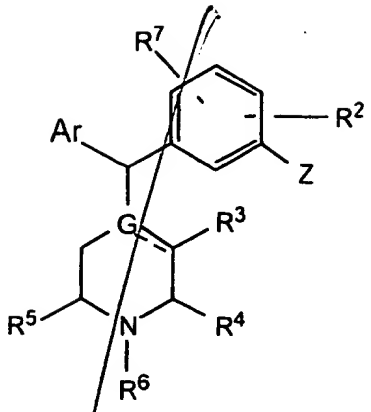
in which $R_{11}$ and $R_{12}$ have the same meaning as $R_9$ and $R_{10}$ or together form an optionally substituted heterocyclic ring and Z is as defined above, and $R_7$ is hydrogen, straight or branched $C_{1-8}$ alkyl or halogen.

25. A pharmaceutical composition according to claim 24, in a form suitable for injectable or spinal administration.

26. A pharmaceutical composition comprising:

(1) an effective amount of a bioactive compound mediating respiratory depression; and

(2) an effective amount of a compound for reducing, treating or preventing respiratory depression, of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent $R^1$,

Y is selected from the group consisting of:

hydrogen;

halogen;

$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;

$C_1$-$C_6$ haloalkyl;

$C_1$-$C_6$ alkoxy;

$C_3$-$C_6$ cycloalkoxy;

sulfides of the formula $SR^8$ where $R^8$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_6$ cycloalkyl, arylalkyl having a $C_5$-$C_{10}$ aryl moiety and an $C_1$-$C_6$ alkyl moiety, or $C_5$-$C_{10}$ aryl;

sulfoxides of the formula $SOR^8$ where $R^8$ is the same as above;

sulfones of the formula $SO_2R^8$ where $R^8$ is the same as above;

nitrile;

$C_1$-$C_6$ acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where $R^8$ is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where $R^9$ and $R^{10}$ may be the same or different, and may be hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_2$-$C_6$ hydroxyalkyl, $C_2$-$C_6$ methoxyalkyl, $C_3$-$C_6$ cycloalkyl, or $C_5$-$C_{10}$ aryl, or $R^9$ and $R^{10}$ together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above, or $C_2$-$C_{30}$ peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

$R^1$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

$R^2$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

$R^3$, $R^4$ and $R^5$ may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of $R^3$, $R^4$ or $R^5$ is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of $R^3$, $R^4$ and $R^5$ together may form a bridge of 1 to 3 carbon atoms;

$R^6$ is selected from the group consisting of:

hydrogen;

$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;

$C_3$-$C_6$ cycloalkyl;

arylalkyl having $C_5$-$C_{10}$ aryl and $C_1$-$C_6$ alkyl moieties;

alkoxyalkyl having $C_1$-$C_4$ alkoxy and $C_1$-$C_4$ alkyl moieties;

$C_2$-$C_4$ cyanoalkyl;

$C_2$-$C_4$ hydroxyalkyl;

aminocarbonylalkyl having a $C_1$-$C_4$ alkyl moiety; and

$R^{12}COR^{13}$, where $R^{12}$ is $C_1$-$C_4$ alkylene, and $R^{13}$ is $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkoxy; and

$R^7$ is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof.

27. A pharmaceutical composition according to claim 26, wherein Ar is a 6-member carbocyclic aromatic (benzene) ring and $R^1$ is hydrogen.

28. A pharmaceutical composition according to claim 26, wherein Y is a carboxamide of the formula $CONR^9R^{10}$.

29. A pharmaceutical composition according to claim 26, wherein $R^9$ and $R^{10}$ together form a ring of five or six atoms, thereby forming a pyrrolidinyl or piperidino ring.

30. A pharmaceutical composition according to claim 26, wherein $R^9$ and $R^{10}$ are the same or different and are each independently selected from hydrogen, $C_1$ alkyl and $C_2$ alkyl.

31. A pharmaceutical composition according to claim 26, wherein Y is hydrogen.

32. A pharmaceutical composition according to claim 26, wherein Y is a sulfone of the formula $SO_2R^8$ and $R^8$ is $C_1$-$C_6$ alkyl.

33. A pharmaceutical composition according to claim 26, wherein G is N, $R^7$ and $R^2$ are each hydrogen, and Z is hydroxyl.

34. A pharmaceutical composition according to claim 26, wherein $R^6$ is selected from the group consisting of hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl and $C_2$-$C_6$ alkynyl.

35. A pharmaceutical composition according to claim 26, wherein $R^3$, $R^4$ and $R^5$ are hydrogen or methyl, where the total number of methyl groups is one or two.

36. A pharmaceutical composition according to claim 26, wherein $R^3$ and $R^5$ are both methyl, and $R^4$ is hydrogen.

37. A pharmaceutical composition according to claim 26, wherein the compound is selected from the group consisting of:

(-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(-)-4-((αR)-α-((2R,5R)-2,5-dimethyl-4-propyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

4-((αR)-α-(2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)benzamide;

N,N-diethyl-4-((αR)-3-hydroxy-α-((2R,5R)-2,5-dimethyl-1-piperazinyl)benzyl)benzamide;

4-((αR)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N-ethyl-N-methyl-benzamide;

3-((αR)- α-((2S, 5S)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-N,N-diethyl-4-((αR*)-3-hydroxy-α-((2R*,5S*)-2,4,5-trimethyl-1-piperazinyl)benzyl)-benzamide;

(+)-4-((αS)-α-((2S,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

3-((αR)-4-(piperidinocarbonyl)- α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

3-((αR)-4-(1-pyrrolidinylcarbonyl)-α-((2S,5S)-2,4,5-trimethyl-1-piperazinyl)benzyl)phenol;

(±)-3-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-4-(methylsulfonyl)benzyl)-phenol;

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfon-amide; or

(-)-4-((αR)-α-((2R,5S)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide,

(±)-3-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)benzyl)phenol;

(±)-4-((αR*)-α-((2S*,5R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxbenzyl)benzamide;

(±)-4-((αR*)-α-((2R*,5S*)-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

(±)-cis-4-(α-(4-allyl-3,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide;

cis-4-(α-(3,5-dimethyl-4-(methylallyl)-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethyl-benzamide;

and pharmaceutically acceptable salts thereof.

38. A pharmaceutical composition according to claim 37, wherein the compound is (-)-4-((αR)-α-((2R,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-diethylbenzamide or a pharmaceutically acceptable salt thereof.

39. A pharmaceutical composition according to claim 26, wherein the bioactive compound comprises an opiate compound.

40. A pharmaceutical composition according to claim 26, wherein the bioactive compound comprises an opiate analgesic compound.

41. A pharmaceutical composition according to claim 26, wherein the bioactive compound comprises a mu opiate compound.

42. A method of treating a patient in need thereof with fentanyl while attenuating fentanyl-induced muscle rigidity and fentanyl-induced respiratory depression, comprising administering to the patient a delta agonist compound in an effective amount to attenuate said fentanyl-induced muscle rigidity and fentanyl-induced respiratory depression.

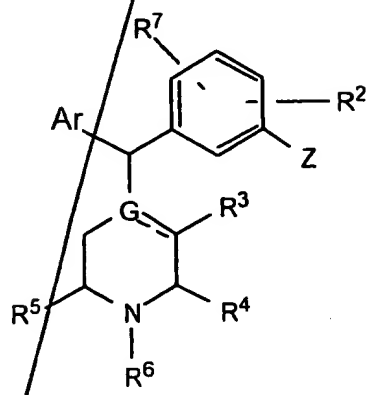
43. A method of treating a patient in need thereof with an opioid receptor therapeutic agent, while attenuating respiratory depression incident to the administration thereof, comprising administering to the patient with said opioid receptor therapeutic agent, a delta agonist compound selected from the group consisting of :

I. [D-Pen$^2$,D-Pen$^5$]-(enkephalin);

II. deltorphin I;

III. deltorphin II;

IV. delta agonist compounds of the formula:



(I)

wherein:

Ar is a 5- or 6-member carbocyclic or heterocyclic aromatic ring with atoms selected from the group consisting of carbon, nitrogen, oxygen and sulfur, and having on a first carbon atom thereof a substituent Y and on a second ring carbon thereof a substituent $R^1$,

Y is selected from the group consisting of:

hydrogen;

halogen;

$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;

$C_1$-$C_6$ haloalkyl;

$C_1$-$C_6$ alkoxy;

$C_3$-$C_6$ cycloalkoxy;

sulfides of the formula $SR^8$ where $R^8$ is $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_6$ cycloalkyl, arylalkyl having a $C_5$-$C_{10}$ aryl moiety and an $C_1$-$C_6$ alkyl moiety, or $C_5$-$C_{10}$ aryl;

sulfoxides of the formula $SOR^8$ where $R^8$ is the same as above;

sulfones of the formula $SO_2R^8$ where $R^8$ is the same as above;

nitrile;

$C_1$-$C_6$ acyl;

alkoxycarbonylamino (carbamoyl) of the formula $NHCO_2R^8$ where $R^8$ is the same as above;

carboxylic acid, or an ester, amide, or salt thereof;

aminomethyl of the formula $CH_2NR^9R^{10}$ where $R^9$ and $R^{10}$ may be the same or different, and may be hydrogen, $C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_2$-$C_6$ hydroxyalkyl, $C_2$-$C_6$ methoxyalkyl, $C_3$-$C_6$ cycloalkyl, or $C_5$-$C_{10}$ aryl, or $R^9$ and $R^{10}$ together may form a ring of 5 or 6 atoms, the ring atoms selected from the group consisting of N and C;

carboxamides of the formula $CONR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above, or $C_2$-$C_{30}$ peptide conjugates thereof; and

sulfonamides of the formula $SO_2NR^9R^{10}$ where $R^9$ and $R^{10}$ are the same as above;

Z is selected from the group consisting of:

hydroxyl, and esters thereof;

hydroxymethyl, and esters thereof; and

amino, and carboxamides and sulfonamides thereof;

G is carbon or nitrogen;

$R^1$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

$R^2$ is hydrogen, halogen, or $C_1$-$C_4$ alkyl, $C_2$-$C_4$ alkenyl, $C_1$-$C_4$ alkynyl;

$R^3$, $R^4$ and $R^5$ may be the same or different, and are independently selected from hydrogen and methyl, and wherein at least one of $R^3$, $R^4$ or $R^5$ is not hydrogen, subject to the proviso that the total number of methyl groups does not exceed two, or any two of $R^3$, $R^4$ and $R^5$ together may form a bridge of 1 to 3 carbon atoms;

$R^6$ is selected from the group consisting of:

hydrogen;

$C_1$-$C_6$ alkyl, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl;

$C_3$-$C_6$ cycloalkyl;

arylalkyl having $C_5$-$C_{10}$ aryl and $C_1$-$C_6$ alkyl moieties;

alkoxyalkyl having $C_1$-$C_4$ alkoxy and $C_1$-$C_4$ alkyl moieties;

$C_2$-$C_4$ cyanoalkyl;

$C_2$-$C_4$ hydroxyalkyl;

aminocarbonylalkyl having a $C_1$-$C_4$ alkyl moiety; and

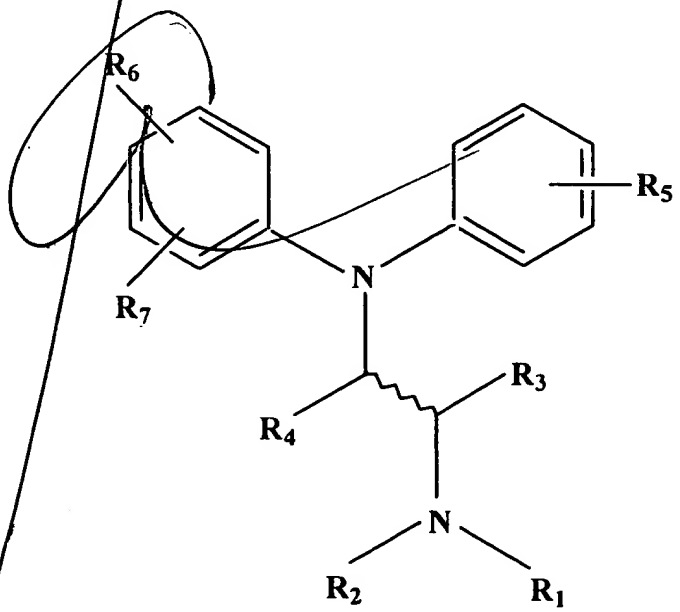
$R^{12}COR^{13}$, where $R^{12}$ is $C_1$-$C_4$ alkylene, and $R^{13}$ is $C_1$-$C_4$ alkyl or $C_1$-$C_4$ alkoxy;

and

$R^7$ is hydrogen or fluorine,

or a pharmaceutically acceptable ester or salt thereof;

V. delta agonist compounds of the formula:




in which,

$R_1$ and $R_2$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{3-7}$ cycloalkenyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, $C_{3-5}$ alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a $C_{3-7}$ alkyl ring which may be interrupted by oxygen.

$R_3$ and $R_4$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl, or $R_4$ is oxygen forming with the carbon atom to which is attached a C=O group;

$R_5$ is hydrogen, hydroxy, $C_{1-3}$ alkoxy, thiol or alkylthio;

$R_6$ is phenyl, halogen, $NH_2$ or a para or meta $-C(Z)-R_8$ group, in which Z is oxygen or sulphur;

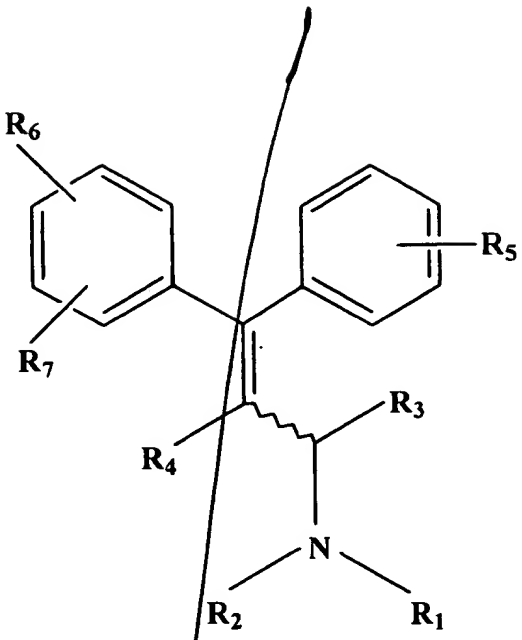
$R_8$ is $C_{1-8}$-alkyl, $C_{1-8}$-alkoxy or $NR_9R_{10}$, wherein $R_9$ and $R_{10}$, which may be the same or different, are hydrogen, straight or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, aryl or aralkyl,

or $R_6$ is a para or meta $-N(R_{11})-C(Z)-R_{12}$ group

in which $R_{11}$ and $R_{12}$ which may the same or different are hydrogen, straight or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, aryl, aralkyl or an optionally substituted heterocyclic ring, and Z is as defined above; and,

$R_7$ is hydrogen, straight or branched $C_{1-8}$ alkyl or halogen; and

VI. delta agonist compounds of the formula:



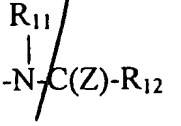

in which,

$R_1$ and $R_2$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{3-7}$ cycloalkenyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, $C_{3-5}$ alkynyl, aryl, aralkyl or furan-2 or 3-yl alkyl or may form together a $C_{3-7}$ alkyl ring which may be interrupted by oxygen.

$R_3$ and $R_4$, which can be the same or different, are each hydrogen, linear or branched $C_{1-6}$ alkyl;

$R_5$ is hydroxy, $C_{1-6}$ alkoxy, thiol or alkylthio;

$R_6$ is a -C(Z)-Rg group, in which Z is oxygen or sulphur, $R_8$ is $C_{1-8}$-alkyl, $C_{1-8}$-alkoxy or $NR_9R_{10}$, wherein $R_9$ and $R_{10}$, which may be the same or different, are hydrogen, straight or branched $C_{1-6}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{4-6}$ cycloalkylalkyl, $C_{3-6}$ alkenyl, aryl or aralkyl,

or $R_6$ is a  group

in which $R_{11}$ and $R_{12}$ have the same meaning as $R_9$ and $R_{10}$ or together form an optionally substituted heterocyclic ring and Z is as defined above, and $R_7$ is hydrogen, straight or branched $C_{1-8}$ alkyl or halogen.

45. A method of reducing, treating or preventing drug-mediated respiratory depression in an animal, incident to the administration to said animal of a respiratory depression-mediating drug, comprising administering to the animal receiving said drug an effective amount of a compound selected from the group consisting of:

(±)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide;

(+)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfon-amide; and

(-)-4-((αR*)-α-((2R*,5S*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-hydroxybenzyl)-N,N-dimethylbenzenesulfonamide, and

pharmaceutically acceptable salts thereof.

46. A method of reducing, treating or preventing drug-mediated respiratory depression, muscle rigidity, or nausea/vomiting in an animal, incident to the administration to said animal of a respiratory depression-mediating drug, comprising administering to the animal receiving said drug an effective amount of a delta receptor agonist or a mixed delta/mu opioid agonist composition.